Osteoporosis: current treatment and future prospects

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Disclosures

- Consultancy and speaking fees for Gilead, related to development of tenofovir alafenamide
- Speaking fees from Amgen/UCB
Approved interventions for osteoporosis

- **Anti-resorptive**
  - Bisphosphonates
  - Denosumab
  - Raloxifene
  - HRT

- **Anabolic**
  - Teriparatide
  - Abalaoparatide*
  - Romosozumab*

* Undergoing regulatory assessment
Bone remodelling

- Resorption
- Reversal
- Resting
- Formation
The bisphosphonates

- Analogues of inorganic pyrophosphate
- Derived from water softening industry: inhibit calcification
- Bind strongly to bone mineral
- Nitrogen-containing BPs inhibit farnesyl pyrophosphate synthase
Mechanism of action of bisphosphonates

- Bisphosphonates inhibit osteoclast activity and promote osteoclast apoptosis.
- Bisphosphonates are released locally during bone resorption.
- Bisphosphonates are concentrated under osteoclasts.
- Bisphosphonates may modulate signaling from osteoblasts to osteoclasts.
  - Increased OPG production
  - Decreased RANKL expression

New bone
Bone
The RANKL/OPG pathway

- CFU-GM
- Prefusion Osteoclast
- Multinucleated Osteoclast
- Activated Osteoclast
- Osteoblasts Osteocytes

Decreased Estrogen Leads to Increased RANK Ligand

Denosumab

- Human antibody to RANK Ligand
- Potent inhibitor of osteoclast development and activity
The Wnt signalling pathway


Absence/reduced sclerostin: Sclerosteosis/van Buchem disease (Balemans et al, 2001, 2002)

(from Patel & Karsenty 2002)
# Approved pharmacological interventions for osteoporosis

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Vertebral (30-70% reduction)</th>
<th>Non-vertebral (15-20% reduction)</th>
<th>Hip (≥ 40% reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate*</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>+</td>
<td>+**</td>
<td>-</td>
</tr>
<tr>
<td>Risedronate*</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Zoledronic acid*</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Denosumab*</td>
<td>+</td>
<td>+</td>
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<tr>
<td>HRT</td>
<td>+</td>
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<tr>
<td>Raloxifene</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Teriparatide*</td>
<td>+</td>
<td>+</td>
<td>-</td>
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</tbody>
</table>

* also approved in men

** post hoc analysis
Dosing regimens of drugs used in the treatment of osteoporosis

**Oral**
- Once daily
  - Raloxifene
- Once weekly
  - Alendronate
  - Risedronate
- Once monthly
  - Ibandronate

**Parenteral**
- Once daily
  - Teriparatide (sc)
- Once 3 monthly
  - Ibandronate (iv)
- Once 6 monthly
  - Denosumab (sc)
- Once yearly
  - Zoledronic acid (iv)
Unmet clinical needs in osteoporosis

- Under-treatment of high risk individuals
- Poor persistence with therapy
- Limited efficacy for some fractures
- Optimal duration of therapy unclear
- “One size fits all” treatment approach
Annualised adjusted probability of osteoporosis medication use after hip fracture age ≥50 yrs

Solomon et al JBMR 2014
Prescription incidence rates of anti-osteoporosis drugs in the UK in women and men age ≥50 years: Clinical Practice Research Datalink

Van der Velde et al Bone 2016
Persistence with anti-osteoporosis medications in postmenopausal women: UK GPRD

1995-2008
Oral BP, raloxifene
or strontium ranelate
N=66,116

Persistence %

<table>
<thead>
<tr>
<th>Time</th>
<th>Persistence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mths</td>
<td>45</td>
</tr>
<tr>
<td>12 mths</td>
<td>30</td>
</tr>
<tr>
<td>36 mths</td>
<td>15</td>
</tr>
<tr>
<td>60 mths</td>
<td>5</td>
</tr>
</tbody>
</table>

Li et al Menopause 2012
Issues relevant to the duration of therapy

• How long does fracture protection persist with treatment?

• Does fracture protection persist after withdrawal of treatment or does fracture risk increase after treatment is stopped?

• What are the potential adverse effects of long-term therapy?
Osteonecrosis of the jaw

- Area of exposed bone in the maxillofacial region that does not heal within 8 weeks after its identification
- No history of radiation therapy to the craniofacial region
- Estimated incidence in patients receiving bisphophonates for osteoporosis: 0.001-0.01%
- Incidence in patients receiving denosumab 0.06% at 3 yrs and 0.44% at 10 years (FREEDOM study)
Atypical femoral fractures

- Associated with anti-resorptive therapy
- Estimated relative risk varies considerably
- Absolute risk is low (for a RR of 47, increase in absolute risk 5 cases per 10,000 patient-years)
- Risk increases with duration of therapy
- High morbidity
Bisphosphonates: algorithm for long-term treatment monitoring

Advise 3-5 yrs* treatment (Follow-up at 3/12 to discuss treatment issues)

No fracture

FRAX + BMD after 3-5* years

Recurrent fracture(s) Prevalent vertebral fracture(s)**

**In patients taking oral BPs, consider continuation if:
- age > 75 yrs,
- previous hip fracture
- current oral GC therapy ≥ 7.5 mg/d prednisolone

Above NOGG intervention threshold or hip BMD T-score ≤-2.5

Check adherence
Exclude 2° causes
Re-evaluate treatment choice
Continue treatment

Below NOGG intervention threshold and hip BMD T-score >-2.5

Consider drug holiday
Repeat FRAX + BMD in 1.5-3 yrs

Compston et al 2014

*3 yrs for zoledronic acid 5 yrs for other BPs
Abaloparatide

- Synthetic analogue of PTHrP (1-34)
- Differs from teriparatide [PTH (1-34)] in weaker binding affinity at the R° conformation of the PTHR1
- Given once daily as sc injection (80 µg)
- FDA approved
Effect of daily abaloparatide in postmenopausal women with osteoporosis: ACTIVE

N=2463, mean age 69 yrs
Treatment duration 18 months

Miller et al JAMA 2016
Effect of abaloparatide on fracture in postmenopausal women: ACTIVE

<table>
<thead>
<tr>
<th></th>
<th>Abaloparatide (80 µg/d sc)</th>
<th>Placebo</th>
<th>Teriparatide (20 µg/d sc)</th>
<th>HR or RR (abalo vs placebo)</th>
<th>P value (abalo vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New vertebral fracture</td>
<td>4 (0.6)</td>
<td>30 (4.2)</td>
<td>6.0 (0.8)</td>
<td>RR 0.14 (0.05,0.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-vertebral fracture</td>
<td>18 (2.7)</td>
<td>33 (4.7)</td>
<td>24 (3.3)</td>
<td>HR 0.57 (0.32, 1.00)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

N=2463, mean age 69 yrs  
Treatment duration 18 months  
Miller et al JAMA 2016
Effect of abaloparatide followed by alendronate: ACTIVExtend trial

(Cosman et al 2017, Mayo Clin Proc)

88% risk reduction in vertebral fracture
Romosozumab

• Monoclonal antibody that binds to and inhibits sclerostin

• Stimulates bone formation and inhibits resorption

• Given as monthly sc injection (210 mg)

• Undergoing regulatory assessment

Effect of romosozumab on BMD in postmenopausal women with osteoporosis: FRAME

210µg sc once monthly

- Placebo (N = 61)
- Romosozumab (N = 62)

Lumbar Spine
Placebo vs romosozumab

Total Hip
Placebo vs romosozumab

* \( p < 0.001 \) compared with placebo. Data are least square means (95% CI) adjusted for relevant baseline covariates.

BMD = bone mineral density; CI = confidence interval; \( \Delta \), difference

Effect of romosozumab on new vertebral fractures in postmenopausal women with osteoporosis: FRAME

n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures; p-value based on logistic regression model adjusted for age (<75, ≥75) and prevalent vertebral fracture.

Effect of romosozumab on new clinical fractures in postmenopausal women: FRAME

Kaplan Meier curve based on data through month 24. Clinical fractures included all nonvertebral and symptomatic vertebral fractures. Non-vertebral fractures comprised the majority (more than 85%) of clinical fractures and excluded fractures of the skull, facial bones, metacarpals, fingers, and toes, pathologic fractures and fractures associated with high trauma. n = number of subjects at risk for event at time point of interest. P-value based on RRR.

ARCH: Active-controlled fracture study in postmenopausal women with osteoporosis at high risk (n=4093)

• Comparison of romosozumab for 1 yr transitioning to alendronate for 1 yr with alendronate alone for 2 yr

• 4093 postmenopausal women with osteoporosis + fragility fracture

• Trial designed to show superiority

• Primary endpoints: vertebral fracture, clinical fracture

• Secondary endpoints: non-vertebral fracture, hip fracture

Saag et al NEJM 2017
Comparative efficacy of romosozumab followed by alendronate vs alendronate alone: ARCH

Saag et al, NEJM 2017

Incidence

HR 0.52
0.4, 0.66

HR 0.73
0.61, 0.88

HR 0.81
0.66, 0.99

HR 0.62
0.42, 0.92

n=4093
Duration 24 months

Vertebral fractures
Clinical fractures
Non-vertebral fractures
Hip fractures

Romo/alendronate
Alendronate

Saag et al, NEJM 2017
The future of anabolic therapies for osteoporosis: what are the issues?

- Speed, extent and sites of fracture reduction: comparative efficacy in high risk individuals
- Limited duration of therapy – benefits need to be maintained thereafter with other drugs
- Cost-effectiveness
- Safety